American Journal of Medical Genetics 62:1–5 (1996)

Brief Clinical Report

Child With Manifestations of Nager Acrofacial Dysostosis, and the MURCS, VACTERL, and Pulmonary Agenesis Associations: Complex Defect of Blastogenesis?

Albert David, Jacques Mercier, and Alain Verloes

Departments of Pediatrics and Human Genetics (A.D.), Clinics of Stomatology and Maxillofacial Surgery (J.M.), CHRU Nantes, France; and Centre for Human Genetics (A.V.), Liège University, Belgium

Nager acrofacial dysostosis (NAFD) combines the facial anomalies of mandibulofacial dysostosis (Treacher-Collins-Francescetti) with hypoplastic/aplastic or triphangeal thumbs. The MURCS association consists of Müllerian duct aplasia, renal aplasia, cervicothoracic somite dysostosis with Klippel-Feil anomaly, and often defects of the facio-auriculo-vertebral (Goldenhar) spectrum. We describe a child with NAFD, MURCS anomaly (Klippel-Feil anomaly, vertebral synostoses, left renal agenesis), and left pulmonary agenesis. Our proband appears to express a unique anomaly of blastogenesis, simultaneously affecting the acrorenal, the mandibulofacial, and the cervicothoracic developmental fields, combining clinical manifestations of the MURCS, NAFD, VACTERL, and pulmonary agenesis associations. All anomalies may be traced back to abnormal blastogenesis, occurring during the third or the fourth week of embryonic development, and show that NAFD is a polytopic developmental field defect.

KEY WORDS: Nager acrofacial dysostosis, MURCS, VACTERL, pulmonary agenesis, blastogenesis, association

INTRODUCTION

Nager acrofacial dysostosis (NAFD) or preaxial acrofacial dysostosis is a relatively common disorder combining the facial anomalies of mandibulofacial dysostosis (Treacher-Collins-Francescetti) with hypoplastic/aplastic or triphangeal thumbs. Sixty-seven cases were collected in a recent critical review of the literature [Opitz et al., 1993]. We report here unusual findings in a case with otherwise typical NAFD syndrome.

CLINICAL REPORT

This patient is the only boy of nonconsanguineous, normal French parents. The father and mother were, respectively, 30 and 23 years old at the birth of the child. Their other child, a girl, was normal. Birth weight, at term, was 2,280 g, length 45 cm, and OFC 33 cm. NAFD was diagnosed at birth. When we saw him at age 5 (Fig. 1a), he was 100 cm tall (−3 SD). The face was triangular (Fig. 1b); the palpebral fissures were not slanted; apparent mild telecanthus was present, with prominent nasal root, flat malar area, microstomia, and severe microretrognathia (Fig. 1c). A posterior cleft palate was corrected, and velopharyngeal incompetence had been treated with pharyngoplasty. The external ears were reduced to low set, anteriorly displaced tags. The meatus was hypoplastic on the right and atretic on the left side. The neck was short, and rotation of the head was impaired. The trunk was normal, except for a mild positional asymmetry of the scapulae. The scrotum was hypoplastic, and testes were incompletely descended. The hands were symmetrically affected: hypoplastic, "floating" thumbs were removed neonatally; the other digits (Fig. 2) and the forearms were normal. The lower limbs were normal, except for flat feet and genua vara. The only neurological anomalies were obvious synkinetic movements of the upper limbs. Internal anomalies included absence of the left lung (Fig. 3) and the left kidney, and normal heart. He had bilateral perceptive deafness. Skeletal survey doc-

Received for publication March 6, 1995; revision received August 31, 1995.

The concepts of abnormal blastogenesis developed in this paper are largely based on the pioneer works of Professor John Opitz on developmental fields. The authors wish to dedicate this work to him on the occasion of his 60th birthday.

Address reprint requests to Dr. A. Verloes, Centre for Human Genetics, CHU Sart Tilman, (B) 4000—Liège, Belgium.

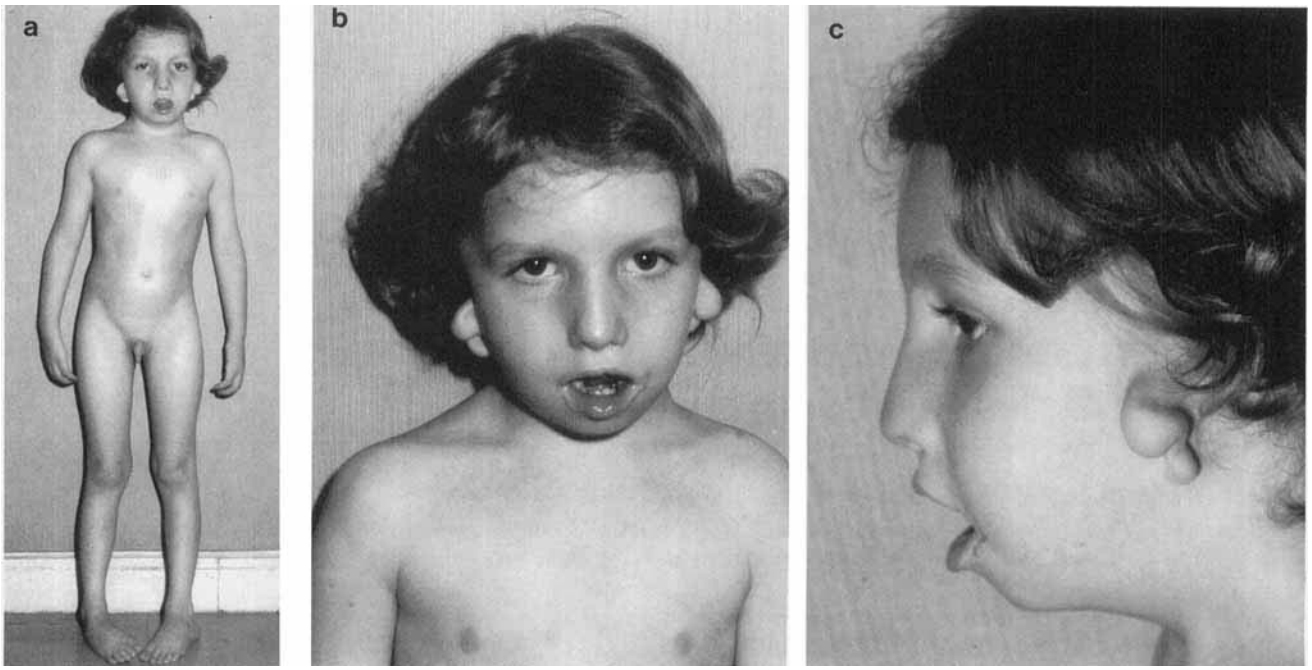

Fig. 1. Clinical aspect of the patient at age 5. **a:** General appearance. **b:** Facial aspect. Note triangular face, microstomia, and short neck. **c:** Profile. Note severe microretrognathia and dysplastic, low-set, anteriorly displaced pinna.

umented Klippel-Feil anomaly with upper cervical block (Fig. 4), atlanto-occipital fusion, and sagittal cleft of the lower cervical spine. Karyotype was normal 46,XY.

Dermatoglyphics

Left hand: II: RL, III: RL, IV: UL, V: UL; no axial triradius, transversality index 24, no opposition crease, distal transverse crease crossing the whole palm. Right hand: II: W, III: UL, IV: UL, V: UL, t′ displacement of the axial triradius, transversality index 36, similar pattern of palmar creases.

At follow-up at age 11½ years, he was 131 cm tall (−2.5 SD), with an OFC of 50.8 cm (−2.5 cm). He wears a hearing aid and attended normal classes at a school for the deaf. He never had respiratory problems or middle ear infections.

DISCUSSION

An association was classically defined as the nonrandom occurrence in 2 or more individuals of multiple anomalies not known to be a polytopic field defect, sequence, or syndrome [Spranger et al., 1982]. An association is an entity that likely reflects environmental events that overlap in time or space, and affect simultaneously developing fields [Lubinsky, 1985], or a pattern of multiple idiopathic anomalies of blastogenesis (the period that extends from karyogamy to the end of gastrulation, at the 28th day of development) [Opitz, 1993]. Although quite convenient in many circumstances, the use of named associations is conceptually limiting by their lack of "natural" boundaries. Contrary to syndromes, which are causally defined entities, the definition of an association requires the causal event (or events, as pathogenic heterogeneity is likely) to occur within a frame of spatial and/or temporal constraints [Duncan, 1977], usually during blastogenesis. The probability of coexistence of two components of an association depends on their topographic or chronological proximity, as it has been demonstrated for the frequencies of signs in VACTERL *association depending* on the cardiac anomaly [Lubinsky and Moeschler, 1987]. Thus, the incidence of each anomaly depends on the absence or presence of others. The causative anomaly could be either genetically programmed or environmentally induced. Two major theories have been proposed to explain the anomalies of blastogenesis. Following the topologic system, the causal event (or events) occurs when the blastemata have intimate spatial relationships [Duncan, 1977]. A single focal hit could result in widely separated anomalies at the end of embryogenesis following direct alteration of the involved blastemata, or through secondary alterations of the induction cascade. With the second hypothesis, the malformed structures derive from an abnormal migration/differentiation process affecting the cells stemming from the primitive streak [Russell et al., 1981] to create the 3 layers of the embryonic mesoderm.

Associated renal and limb malformations are referred to as acrorenal field defects [ARFD; Curran and Curran, 1972; Dieker and Opitz, 1969]. Acral defects affect either the lower or the upper limbs, or both, and are usually asymmetric or unilateral. Malformations are extremely variable, although cleft hand/foot are the most common manifestations. Mandibulofacial dysostosis does not belong to the ARFD spectrum, but mi-

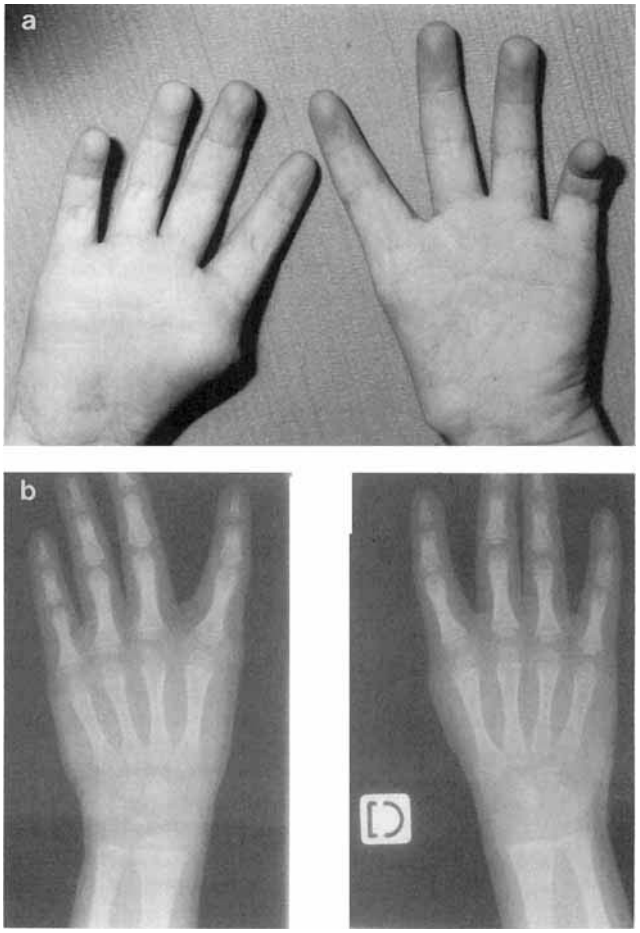

Fig. 2. Post-surgical appearance of the hands **(a)** and corresponding radiography **(b)**.

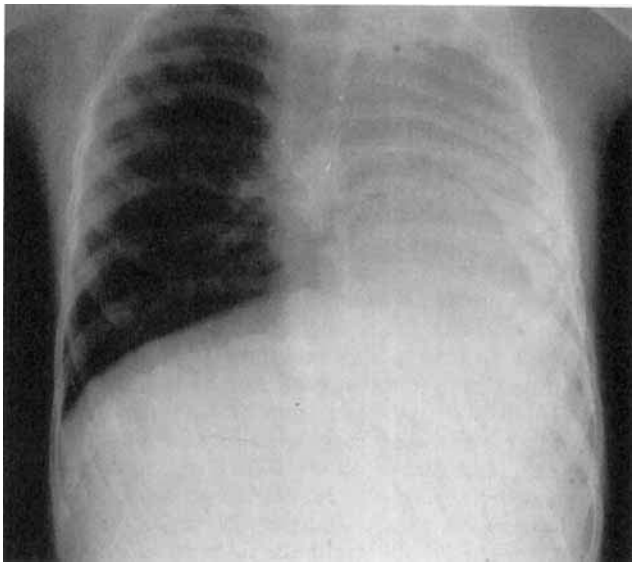

Fig. 3. Chest X-ray: total absence of left lung.

crognathia was present in some cases [Curran and Curran, 1972]. ARFD occurs as a sporadic primary defect, or as a component of several multiple congenital anomalies (MCA) syndromes. Depending on the syndromal context, the acral and renal components of ARFD appear to be unequally weighted (e.g., see the relative frequencies of both manifestations in Weyers oligodactyly vs. Fanconi anemia).

Klippel-Feil anomaly is characterized by fusion of 2 or more cervical vertebrae. Clinically, its manifestations include short neck, limited head rotation, and low posterior hairline. Synkinetic movements are commonly observed with Klippel-Feil anomaly. Cleft palate occurs in 16% [Gorlin et al., 1990] and kidney anomalies (agenesis, horseshoe kidney) in 35% [Hensinger et al., 1974]. The MURCS association consists of Müllerian duct aplasia (Rokitansky-Küster-Hauser urogenital adysplasia), renal agenesis/ectopia, and cervicothoracic somite dysostosis with Klippel-Feil anomaly, abnormal ribs, and Sprengel deformity [Duncan et al., 1979]. Several facial anomalies of Goldenhar facio-auriculo-vertebral spectrum (FAVS) may occur with MURCS association [Wulfsberg and Grigsby, 1990; Winer-Muram et al., 1984]. The symmetry of the facial anomalies, the microstomia, and the malar hypoplasia observed in our propositus do not fit well a diagnosis of FAVS. Moreover, radial defects and lung aplasia do not enter the usual spectrum of MURCS, although each of them has been mentioned once among 50 cases [Hensinger et al., 1974]. Unfortunately, the patients in this latter review were not described individually, nor analyzed from a syndromic perspective. Other rare anomalies of the arm reported with MURCS include ulnar ray aplasia [Chemke et al., 1980] and unilateral upper limb hypoplasia [Hensinger et al., 1974]. The probably recessively inherited acrorenomandibular syndrome [Halal et al., 1980] consists of split hand/foot malformation,

Fig. 4. Profile view of the cervical spine showing segmentation defects.

uterine anomalies, renal agenesis or cystic dysplasia, and extreme micrognathia. Chemke et al. [1980] described a sporadic occurrence of Klippel-Feil anomaly, Sprengel deformity, preauricular appendage, and absent ulna. Although those case reports illustrate that MURCS and ARFD may occur concurrently, and constitute the basis of a broader "acro-cervico-reno-genital" polytopic field defect, they still do not encompass the spectrum of anomalies observed in our patient.

NAFD is a heterogeneous entity associating a more or less pronounced complex of acrofacial anomalies that may be designated generically as mandibulofacial dysostosis, as well as limb anomalies, usually confined to the upper limb and its preaxial area or field [Opitz et al., 1993]. From this paper and other reviews [Gorlin et al., 1990; Pfeiffer and Stoess, 1983; Halal et al., 1983; McDonald and Gorski, 1993], NAFD appeared initially to be a suitable diagnosis for our propositus. Pathogenesis of NAFD is poorly understood. Opitz [1993], who uses the term Nager anomaly instead of Nager syndrome, considers NAFD a causally heterogeneous polytopic developmental field defect affecting both craniofacial neural crest development and the limb field. This interpretation still lacks experimental embryological evidence of a functional link between the 2 involved areas, such as a common inductor. Expressivity of NAFD varies from minimal acrofacial signs to the lethal form initially described by Kawira et al. [1984]. The latter is clearly linked to the common form by rare familial observations where both phenotypes were observed [LeMerrer et al., 1989]. Despite this large variability of the acrofacial anomalies, associated malformations are unusual in NAFD. Opitz et al. [1993] consider them variable, probably coincidental or due to ascertainment bias, although others [McDonald and Gorski, 1993] include several malformations in the clinical spectrum of NAFD, such as cervical vertebral anomalies [Jones, 1968] and costal anomalies [Halal et al., 1983]. Though rare, renal anomalies were encountered in several reports of NAFD [patient 17 in Pfeiffer, 1969; Pfeiffer and Stoess, 1983; Halal et al., 1983]. This suggests that the renal anomalies could be a component of NAFD.

At least 173 cases of unilateral pulmonary agenesis were reported by 1968, and the excellent reviews of the literature published at that time have not been updated [Oyamada et al., 1953; Booth and Berry, 1967; Maltz and Nadas, 1968]. In 23% of the cases there were cardiac or vascular anomalies, in 14% gastrointestinal anomalies (tracheoesophageal fistula and/or imperforate anus), in 5% fused vertebrae or hemivertebrae (often at the upper thoracic level), and in 9% urogenital anomalies (renal agenesis, horseshoe kidney, hemiuterus) [Maltz and Nadas, 1968]. Radial anomalies were present in many of them [Osborne et al., 1989]. Remarkably, visceral and acral anomalies tend to be ipsilateral to the missing lung. Many of those cases would now fall into a diagnosis of VACTERL association, although its spectrum ascertained through pulmonary agenesis could differ considerably, in relative frequencies, from the common VACTERL association (as the spectrum of anomalies associated with tracheal agenesis differs from the usual VACTERL association [Evans et al., 1985] in relative frequencies). Several cases of unilateral pulmonary agenesis were observed with ipsilateral craniofacial anomalies, such as, microtia [patient 3 in Ferguson and Neuhauser, 1944], facial asymmetry, or other anomalies clearly pertaining to the FAVS [patient 13 in Booth and Berry, 1967]. Patient 5 of Field [1946] had left pulmonary agenesis, tracheal stenosis, cleft palate, cervical spine malformation, and heart defect. Although published as mandibulofacial dysostosis, the patient described by Wilson [1958] had hemifacial microsomia and lung agenesis. A patient of Opitz and Faith [1969] was similarly affected.

Some case reports combine anomalies observed in our propositus. Patient MD of Maltz and Nadas [1968], briefly described, had right lung aplasia, agenesis of the right kidney, deformed ears, multiple abnormalities of ribs and vertebrae, and hypertelorism. Rapin and Ruben [1974] described a girl with left hemifacial microsomia, abnormal cervical and thoracic spine, anal malformation, Müllerian aplasia, left kidney agenesis, and right radial ray hypoplasia. Patient 14 of Booth and Berry [1967] showing apparently hypoplastic digitalized thumb and malar hypoplasia, associated with pulmonary agenesis, could have mild NAFD. Bilateral pulmonary agenesis was observed with microstomia and micrognathia, tracheoesophageal fistula, left renal hypoplasia, and imperforate anus in patient 2 of DeBuse and Morris [1973]. Case 1 of Smith and Bech [1958] presented with absence of the right lung, esophageal atresia, bilateral shapeless rudimentary pinnae, and right radial agenesis, hence being possibly a case of NAFD-VACTERL compound. None of those reports encompass the complete phenotype of our propositus.

Russell et al. [1981] proposed the concept of axial mesodermal dysplasia or mesodermal malformation spectrum [Wulfsberg and Grigsby, 1990] to encompass FAVS, MURCS, Wildervanck syndrome, VACTERL association, caudal regression, renal agenesis, and femorofacial syndrome. Whatever the pathogenetic nature of his entity, our patient shows one of the most complex expressions of this mesodermal malformation spectrum, and let question the accuracy of this concept, as anomalies in this child involve much more than the mesoderm. The mesodermal malformation spectrum largely overlaps with the concept of anomaly of the blastogenesis, as defined by Opitz. Our patient clearly has an anomaly of blastogenesis, occurring during gastrulation, that simultaneously affected the acrorenal, the mandibulofacial, and the cervicothoracic developmental fields, thus encompassing VACTERL, NAFD, and MURCS associations. All anomalies may be traced back to the third (first somites) or the fourth week of embryonic development (appearance of lungs and upper limb buds, nephrogenesis).

Since most cases of NAFD are sporadic and since its clinical manifestations clearly represent a disorder of blastogenesis, we suggest that NAFD syndrome, in its common acception, should be seen as a phenotype, or more precisely, a complex (or anomaly). The Nager complex is causally heterogeneous. True Nager syndrome corresponds to the rare cases with autosomal dominant

or autosomal recessive inheritance. For those cases, the spectrum of observed defects results from the pleiotropic action of a yet unknown developmental gene. Nevertheless, most cases appear not to be genetically determined. All anomalies observed in our patient beyond the spectrum of NAFD are all field defects, all notoriously causally heterogeneous, and all observed in associations. Absence of minor anomalies and normal IQ are arguments to suspect his pattern of anomalies to be due to a single hit during blastogenesis, rather than through pleiotropy or aneuploidy. Since the NAFD complex itself involves 2 defects of morphogenesis (abnormal blastogenesis and abnormal organogenesis), and since it occurred here in a patient with an association, it fits the definition of a polytopic field defect [by contrast, monotopic field defects usually are only disturbances of organogenesis; Opitz, 1993, 1994].

In summary, phenotype analysis of our patient contributes important points to the nosology of NAFD. Since NAFD occurred in a boy with an association, it is shown to be a defect of blastogenesis, and confirmed as a polytopic field defect. Defining associations is a rather arbitrary or subjective exercise. In this case, it makes little sense to choose one association over another as the diagnosis, since our patient clearly presents as a compound of all of them (NAFD, MURCS, VATER, FAVS).

REFERENCES

Booth JB, Berry CL (1967): Unilateral pulmonary agenesis. Arch Dis Child 42:361–374.

Chemke J, Nisani R, Fischel RE (1980): Absent ulna in the Klippel-Feil syndrome: An unusual associated malformation. Clin Genet 17:167–170.

Curran AS, Curran JP (1972): Associated acral and renal malformations: A new syndrome? Pediatrics 49:716–725.

DeBuse PJ, Morris G (1973): Bilateral pulmonary agenesis, oesophageal atresia, and the first arch syndrome. Thorax 28:526–528.

Dieker H, Opitz JM (1969): Associated acral and renal malformations. BD:OAS V(3):68–77.

Duncan PA (1977): Embryologic pathogenesis of renal agenesis associated with cervical vertebral anomalies (Klippel-Feil phenotype). BD:OAS 13(3D):91–101.

Duncan PA, Shapiro LR, Stangel JJ (1979): The MURCS association: Mullerian duct aplasia, renal aplasia, and cervicothoracic somite dysplasia. J Pediatr 95:399–402.

Evans JA, Reggins J, Greenberg C (1985): Tracheal agenesis and associated malformations: A comparison with tracheoesophageal fistula and the VACTERL association. Am J Med Genet 21:21–24.

Ferguson CF, Neuhauser BD (1944): Congenital absence of the lung (agenesis) and other anomalies of the tracheobronchial tree. Am J Roentgen Radiat Ther 52:459–471.

Field CE (1946): Pulmonary agenesis and hypoplasia. Arch Dis Child 21:61–75.

Gorlin RJ, Cohen MM, Levin LS (1990): "Syndromes of the Head and Neck," 3rd ed. New York: Oxford University Press.

Halal F, Desgranges MF, Leduc B, Théorêt G, Bettez P (1980): Acro-renal-mandibular syndrome. Am J Med Genet 5:277–284.

Halal F, Herrmann J, Pallister PD, Opitz JM, Desgranges MF, Grenier G (1983): Differential diagnosis of Nager acrofacial dysostosis syndrome: Report of four patients with Nager syndrome and discussion of other related syndromes. Am J Med Genet 14:209–224.

Hensinger RN, Lang JE, McEwen D (1974): Klippel-Feil syndrome: A constellation of associated anomalies. J Bone Joint Surg A 56:1246–1253.

Jones G (1968): Mandibulofacial dysostosis. Cent Afr J Med 14:255–260.

Kawira EL, Weaver DD, Bender HA (1984): Acrofacial dysostosis with severe facial clefting and limb reduction. Am J Med Genet 17:641–647.

LeMerrer M, Cikuli M, Ribier J, Briard ML (1989): Acrofacial dysostoses. Am J Med Genet 33:318–322.

Lubinsky M (1985): Associations in clinical genetics with a comment on the paper by Evans et al on tracheal agenesis. Am J Med Genet 21:35–38.

Lubinsky M, Moeschler J (1987): Different clusters within the VATER association distinguished through cardiac defects: Possible effects of teratologic timing? Dysmorphol Clin Genet 1:80–82.

Maltz DL, Nadas AS (1968): Agenesis of the lung: Presentation of eight new cases and review of the literature. Pediatrics 42:175–187.

McDonald MT, Gorski JL (1993): Nager acrofacial dysostosis. J Med Genet 30:779–782.

Opitz JM (1993): Blastogenesis and the "Primary Field" in Human Development. New York: Alan R. Liss, Inc., for the National Foundation—March of Dimes. BD:OAS XXIX(1):3–37.

Opitz JM (1994): Associations and syndromes: Terminology in clinical genetics and birth defects epidemiology: Comments on Khoury, Moore and Evans. Am J Med Genet 49:14–20.

Opitz JM, Faith GC (1969): Visceral anomalies in an infant with Goldenhar syndrome. Birth Defects: OAS V(2):104–105.

Opitz JM, Mollica F, Sorge G, Milana G, Cimino G, Caltabiano M (1993): Acrofacial dysostoses: Review and report of a previously undescribed condition: The autosomal or X-linked dominant Catania form of acrofacial dysostosis. Am J Med Genet 47:660–678.

Osborne J, Masel J, McCredie J (1989): A spectrum of skeletal anomalies associated with pulmonary agenesis: Possible neural crest injuries. Pediatr Radiol 19:425–432.

Oyamada A, Gasul BM, Holinger PH (1953): Agenesis of the lung. Am J Dis Child 85:182–201.

Pfeiffer RA (1969): Associated deformities of the head and hands. BD:OAS V(3):18–34.

Pfeiffer RA, Stoess H (1983): Acrofacial dysostosis (Nager syndrome): Synopsis and review of a new case. Am J Med Genet 15:255–260.

Rapin I, Ruben RJ (1974): Patterns of anomalies in children with malformed ears. Laryngoscope 86:1469–1502.

Russell LJ, Weaver DD, Bull MJ (1981): The axial mesodermal dysplasia. Pediatrics 67:176–182.

Smith RA, Bech AO (1958): Agenesis of the lung. Thorax 13:28–33.

Spranger J, Bernischke K, Hall JG, Lenz W, Lowry BD, Opitz JM, Pinsky L, Schwarzacher HG, Smith DW (1982): Errors of morphogenesis: Concepts an term. J Pediatr 100:160–165.

Wilson TG (1958): A case of unilateral mandibulo-facial dysostosis associated with agenesis of the homolateral lung. J Laryngol 72:238–249.

Winer-Muram HT, Muram D, Wilroy RS, Cupp C (1984): The concurrence of facioauriculovertebral spectrum and the Rokitansky syndrome. Am J Obstet Gynecol 149:569–570.

Wulfsberg EA, Grigsby TM (1990): Rokitansky sequence in association with the facio-auriculo-vertebral sequence: Part of a mesodermal malformation spectrum? Am J Med Genet 37:100–102.